

Scientific and Clinical Advances Advisory Committee (SCAAC) - minutes

Date of meeting: 21st October 2015

Location: Etc. Venues Tenter House, 45 Moorfields, London EC2Y 9AE

Committee members	Present	Sue Price (Chair) Kate Brian Yacoub Khalaf Andy Greenfield	
	Apologies	Sally Cheshire Alan Thornhill	
External Advisors		Daniel Brison Joyce Harper Raj Mathur Gudrun Moore Jane Blower	Robin Lovell-Badge Melanie Davies Sheena Lewis
Members of executive		Sarah Testori (lead) Anna Quinn (secretary) Hannah Verdin Nick Jones Peter Thompson	
Invited Speakers		Prof Andy Vail Prof Roy Homburg Dr Sarah Armstrong	
Observers		Steve Pugh Dr Priya Bhide	

1. Welcome, apologies and declarations of interest

- 1.1.** The Chair welcomed committee members to the meeting and introduced Anna Quinn as the new Scientific Policy Officer at the HFEA. Steve Pugh was welcomed as an observer.
- 1.2.** The Chair conveyed apologies on behalf of Sally Cheshire and Alan Thornhill. The Chair also noted that this would have been Alan's last SCAAC meeting and thanked him for his work on the committee.
- 1.3.** Peter noted that this would be Sue's last SCAAC meeting and thanked her on behalf of the HFEA and Sally Cheshire for her contribution to the committee and for her work as Chair.
- 1.4.** In relation to the meeting agenda, interests were declared by Melanie Davies who has a research interest in health outcomes in children conceived using assisted reproductive technologies; and by Daniel Brison who has research interests in health outcomes of IVF children and culture media and has advised manufacturers of time-lapse imaging incubators in his capacity as an IVF Scientific Director.

2. Matters Arising

- 2.1.** Minutes of the meeting held on 10 June 2015 were agreed remotely prior to the meeting.
- 2.2.** Some members of the committee requested that the British Fertility Society be sent the final versions of the HFEA patient information, via Joyce and Raj, as they are also currently working on patient information in this area.
- 2.3.** The committee suggested that ethical implications of next generation sequencing should be considered by the Authority alongside SNP based techniques such as karyomapping, as technology is progressing very quickly in this field.
- 2.4.** The committee was informed that there are currently three National Institute for Health Research funded clinical trials currently taking place in the UK. The first is looking at selecting sperm for ICSI and is approximately two thirds of the way through recruitment; the second trial relates to freeze-all cycles and recruitment is due to start by early 2016; the third trial is looking at endometrial scratching and staggered recruitment is currently being considered to avoid co-recruitment with the freeze-all trial. The committee noted that it would be useful for information about these trials to be available to patients on the HFEA website
- 2.5.** The committee requested to see the wording of the Code of Practice guidance notes on PGS before it is introduced into the next revision of the Code in April 2016.

Actions:

- 2.6.** The Scientific Policy Manager will resend the data showing the total number of PGS cycles that have been conducted between 2012 and 2013 to the committee.
- 2.7.** The Scientific Policy Manager will circulate the final wording of the revised Code of Practice PGS guidance note to the committee for information.
- 2.8.** The Scientific Policy Manager will circulate the executive's letter in response to a paper regarding the overuse of calcium ionophore in culture medium.

- 2.9.** The Executive will send draft PGS patient information to the committee for comment.
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3. Chair's Business

- 3.1.** The Chair requested that committee self-evaluation forms be completed and returned during the day, or completed after the meeting and returned by email to the Scientific Policy Officer as soon as possible as comments need to be collated by the end of the year.
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4. Committee Work Plan

- 4.1.** The committee agreed which members would take responsibility for checking each of the horizon scanning spreadsheet tabs.
- 4.2.** The Chair clarified that the horizon scanning spreadsheet will be sent to the committee six weeks before the February 2016 meeting, comments will be requested by three weeks prior to the meeting to be collated and incorporated into the materials for the meeting.
- 4.3.** The committee considered topics that could be presented by an invited speaker at the February 2016 meeting. In vitro maturation and simplified IVF were suggested and a speaker will be invited based on availability.
- 4.4.** The committee agreed that new technologies in genetic testing should become a standing item for consideration and that an annual, objective literature review should be presented. The committee noted that it will be important to clarify whether the committee is discussing the techniques themselves or the ethical issues surrounding their use. The committee agreed that unbiased information on the HFEA website about the evidence in this area and equipping patients with questions that could be asked in the clinic would be useful for patients. The committee also agreed that embryo biopsy and cryopreservation could fall under this item.
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5. Embryo culture medium update

- 5.1.** The Scientific Policy Manager presented a paper summarising recent studies investigating the impact of varying components in culture media. This was an update since the committee last considered embryo culture media in February 2014. Members were asked to consider the progress of research into the effects of the components in culture media used for IVF treatment, advise the executive if they are aware of any other recent developments and reflect on their views to date and identify what needs to be communicated to the MHRA.
- 5.2.** Since the committee last reviewed the impacts of culture media, numerous studies have been published in this area with most of the research examining the impact of culture conditions on birth weight. Despite the large number of published studies in recent years, research into the impacts of culture media remains inconclusive. More rigorously designed, large-scale randomised-controlled trials are needed to make firm conclusions on the impact of culture media and more general culture conditions, and these should investigate the effects of culture media on a range of end-points including long-term health outcomes.
- 5.3.** The committee asked about links with the MHRA and their position as registered experts as there has been little communication since a joint meeting three to four years ago. The executive agreed to clarify the links when the culture media paper is sent to the MHRA. Members were asked to

submit any comments on the culture media paper within two weeks of the meeting so they can be collated and applied to the paper.

- 5.4.** The committee expressed an interest in seeing a paper or inviting a speaker to talk about Hyaluronin/Embryo Glue.
- 5.5.** Committee members expressed concerns about post market surveillance and lack of reporting from IVF clinics.

Action

- 5.6.** The scientific policy manager will clarify the status of links between the executive, SCAAC and the MHRA when the culture media paper is sent by email to the MHRA. The status of links will be reported to the committee at the February meeting.

6. Time-lapse imaging

- 6.1.** Three speakers were invited to present to the committee about time-lapse imaging; Professor Roy Homburg, Dr Sarah Armstrong and Professor Andy Vail.
- 6.2.** Professor Roy Homburg presented on the topic of time-lapse imaging and an upcoming randomised clinic trial in this area. Professor Homburg noted that success rates for ICSI are suboptimal and have remained static over recent years. It was also pointed out that standard methods of embryo selection have poor predictive accuracy and further research into embryo selection has been recommended.
- 6.3.** Time-lapse imaging is a technique that allows embryos to be monitored without being removed from the incubator. A camera built into the incubator records a series of images that are then used to help select the best quality embryos to transfer. There is currently no standard algorithm for selecting embryos for transfer following time-lapse imaging. The hoped benefits of time-lapse imaging for embryo selection included improved live birth rate, reduced time to pregnancy per couple, increased elective single embryo transfer (and benefits associated with a subsequent reduction in multiple pregnancy rates) and economic benefits.
- 6.4.** Professor Homburg stated that a large, randomised controlled trial on time-lapse imaging is necessary in the UK to determine if there is an effect of time-lapse imaging on live birth rate, to have a study that has relevance to the local UK population, to carry out a health economic evaluation of time-lapse imaging and to produce long term safety data.
- 6.5.** The committee was informed that an application for funding has been made for a randomised trial aiming to ascertain if time-lapse imaging is clinically and economically more effective than standard care in improving the live birth rate following IVF/ICSI. The proposed study will be randomised in design with three arms, one using time-lapse imaging, one using undisturbed culture and a final control group using standard care. Primary outcome of the proposed study is healthy live birth rate with target recruitment of 1620 patients (520 patients per treatment group).
- 6.6.** The presentation was concluded by summarising why patients and clinicians are in favour of time-lapse imaging. Clinicians agree that the technique does no harm and helps to demystify embryology. Patients are in favour of the technique as they can understand the theoretical benefit of undisturbed culture, they approve of utilising new technology and they can obtain images of

their early stage embryos. Finally, it was concluded that time-lapse will at the very least, enhance reproductive knowledge.

- 6.7.** Professor Andy Vail presented on the topic of how to assess time-lapse imaging. The committee was informed about methodological approaches to assessing complex interventions such as time-lapse imaging. Theoretical studies were categorised into 'Type 1', 'Type 2' and 'Type 3' studies. Type 1 studies look at culture conditions, comparing the time-lapse imaging incubator to current routine practice. Type 2 studies examine cell tracking algorithms, comparing time-lapse imaging with and without an algorithm. Type 3 studies compare the use of time-lapse imaging using an algorithm with current routine practice. Current literature on time-lapse imaging was categorised into these groups and it was concluded that studies in this area range across the different study types discussed.
- 6.8.** Dr Sarah Armstrong gave a presentation about the current randomised controlled trial evidence on time-lapse systems. A systematic review was carried out by the Cochrane Gynaecology and Fertility group which identified three randomised controlled trials that were eligible for inclusion and one more study has been identified since publication of the review. Following assessment the quality of these studies was deemed to be low to moderate. Two studies were 'Type 1' in design and two were 'Type 3' in design. The review concluded that there is insufficient evidence of differences in live birth, miscarriage, still birth or clinic pregnancy between time-lapse imaging and conventional incubation.
- 6.9.** The committee noted that that the time-lapse incubators are high quality incubators even without using an algorithm to analyse time-lapse images and that many clinics are already committed to using this technology which may confound clinical trials in this area. Members also pointed out that some clinics do not charge patients when time-lapse incubators are used as using this technology can reduce costs for the clinic. Whether NHS patients can be charged for this technology was also discussed.
- 6.10.** The committee discussed the additional information that becomes available to clinicians when time-lapse imaging is used and the benefits of having undisturbed culture. Members discussed whether providing videos of preimplantation embryos is increasing patient expectations or whether having the video may provide comfort when a cycle is unsuccessful.
- 6.11.** The committee agreed that even if a clinical trial shows no improvement in live birth rate with time-lapse imaging, these incubators are good pieces of equipment that provide potentially useful information that increase our knowledge of embryo development.
- 6.12.** The committee asked the speakers whether adding a positive result of the Time Lapse Imaging Trial (TILT) would influence the result of the meta-analysis. Speakers agreed that a positive result may not push the results of the meta-analysis to statistical significance, however a well conducted randomised trial may provide better evidence than a meta-analysis that combines studies with high heterogeneity.
- 6.13.** Committee members agreed that it would be useful to have some patient information about time-lapse imaging on the HFEA website and felt that sufficient information had been provided to enable the executive to produce a draft.

Action:

- 6.14.** The executive will draft patient information about time-lapse imaging for the HFEA website.

7. Health outcomes in children conceived using assisted reproductive technologies

- 7.1.** The Scientific Policy Manager presented a paper summarising recent studies on health outcomes in children conceived using assisted reproductive technologies published between October 2013 and October 2015. Members were asked to consider any areas of work in further detail or monitor any areas for particular attention and consider reviewing information clinics are required to make available to patients and the information the HFEA makes available to patients.
- 7.2.** Since October 2013 a large number of studies have been carried out in this area. Of the studies included in the paper, 16 indicated that ART technologies are associated with an increased risk of adverse health outcomes, six studies found no relationship between ART and health outcomes and two studies compared different ART techniques with no control group of spontaneously conceived children.
- 7.3.** The committee discussed that quality of data and noted that much of the research in this area involved small sample sizes meaning that results must be interpreted with caution. The committee agreed that these studies should still be presented to have an overview of all the research being carried out in the field, however it was suggested that impact factor of the publishing journals should be taken into account when compiling literature reviews in future.
- 7.4.** One of the committee members sent an additional list of studies that have been published regarding health outcomes in children conceived using ART, this list can be found as an annex to these minutes.
- 7.5.** The committee noted that it was difficult to differentiate between the risks to babies of fertility treatment and the risks associated with innate parental factors such as underlying fertility problems or other health problems such as obesity or underlying infertility.
- 7.6.** The committee agreed that it is important to keep monitoring research in health outcomes as the field is very fast moving.
- 7.7.** The committee noted that it has been well established that IVF babies are more likely to have a lower birthweight than naturally conceived babies. Members discussed whether the HFEA website should provide information about effects of ART using fresh embryos on birth weight and subsequent adverse health outcomes related to lower birth weight. Some members pointed out that whilst on average children born following fresh embryo transfer have lower birth weight than spontaneously conceived children, this group may not have an increased proportion of babies who are clinically defined as having low birth weight. The committee agreed that it would be useful to obtain growth curves for ART babies compared with naturally conceived when this data becomes available.
- 7.8.** The committee agreed that some patient information about birth weights should be drafted, using the ESHRE wording as a guide, with a view to putting this information on the HFEA website. It was also agreed that there is no need to have a requirement in the Code of Practice for clinics to provide additional information about this to patients. The Committee discussed how to give clinics guidance on how to pass information about risk onto patients, including personal and population risk.

Action:

- 7.9.** Draft some patient information about birth weights for the HFEA website that will be updated once growth curves for the UK population have been published in 2016.
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8. Any other business

- 8.1.** The committee was updated on recent activities of the Nuffield Council on Bioethics and their approach to considering genome editing along with an update on the activities of the Hinxtion Group relating to genome editing.
- 8.2.** One member requested that preparing patient information about the potential impacts of genetic testing on donors, donor conceived children and their parents should be discussed. The committee agreed that this could be added to their annual look at developments in genetic testing.
- 8.3.** The committee was asked for its views on how egg freezing data should be in the next HFEA trends and figures report. Some members expressed that they had information that could be shared with the executive regarding egg freezing. The committee agreed with the suggested data items/tables for the report. The committee discussed a paper recently published regarding pluripotent stem cells.
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9. Meeting Summary

- 9.1.** The Chair thanked the committee for a productive meeting and reminded members to complete their committee evaluation forms.
- 9.2.** Committee members thanked Sue for her contribution to SCAAC.
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10. Next meeting:

- 10.1.** The next Committee meeting will be held on 3rd February 2016.

Signature *Susan Price*

Name Susan Price

Position: Committee chair

Date 11-12-2015

Annex – Additional references

Embryo Quality

- The phenotype of an IVF child is associated with peri-conception measures of follicular characteristics and embryo quality. (Green et al 2014)
- Birth weight in IVF singleton births is not associated with blastocyst quality (Stewart 2015) SUPPLEMENT
- Birth weight is associated with inner cell mass grade of blastocysts (Licciardi et al 2015)

Extended Embryo Culture

- Male gender explains increased birthweight in children born after transfer of blastocysts (Kaartinen 2015)

Number of Oocytes Retrieved

- Increased risk of preterm birth and low birthweight with very high number of oocytes following IVF: an analysis of 65 868 singleton live birth outcomes (Sunkara et al 2015)

IVF vs Natural

- Influence of in vitro fertilization and embryo transfer on the physical and intellectual development of the children at pre-school age. (Zuo et al 2014) ABSTRACT: <http://europepmc.org/abstract/med/25512286>
- Singleton birth weight by gestational age following in vitro fertilization in the United States (Dickey et al 2015)
- Association of in vitro fertilization with global and IGF2/H19 methylation variation in newborn twins (Loke 2015)
- Asthma and asthma medication use among 4-year-old offspring of subfertile couples – association with IVF? (Kuiper et al 2015)
- Right ventricular dysfunction in children and adolescents conceived by assisted reproductive technologies (von Arx 2015)
- Long term prognosis of children born through assisted reproductive technologies in Japan (Kojima et al 2015) (SUPPLEMENT)]
- Perinatal outcomes associated with assisted reproductive technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART) (Declercq et al 2015)

Fresh vs FET

- Changes in singleton live birth weights in a large IVF practice over an 18 year period. (Maas et al 2015) (SUPPLEMENT)
- Difference in birth weight of consecutive sibling singletons is not found in oocyte donation when comparing fresh versus frozen embryo replacements (Galliano 2015)
- Surveillance of congenital malformations in infants conceived through assisted reproductive technology or other fertility treatments (Heisy et al 2015)
- Effect of embryo freezing on perinatal outcome after assisted reproduction techniques: lessons from the Latin American Registry of Assisted Reproduction (Schwarze 2015)

- Siblings conceived with assisted reproductive technology: birthweight and gestation differences in fresh vs frozen cycles (Luke, Wantman et al 2015) (SUPPLEMENT)

Birth Defects

- Comparison of live-birth defects after luteal-phase ovarian stimulation vs. conventional ovarian stimulation for in vitro fertilization and vitrified embryo transfer cycles (Chen et al 2015)
- Neonatal complications and birth defects in infants conceived by in vitro fertilization (Xy et al 2015)
ABSTRACT: <http://europepmc.org/abstract/med/25919554>
- Birth defects after assisted reproductive technology according to the method of treatment in Japan: nationwide data between 2004 and 2012 (Ooki et al 2015)

ADHD

- I was born following ART: how will I get on at school? (Abdel-Mannan & Sutcliffe 2014)